

CO-OPERATIVE EVALUATION OF TREATMENT FOR EARLY SYPHILIS*

PRELIMINARY REPORT WITH SPECIAL REFERENCE TO SPECTINOMYCIN SULPHATE (ACTINOSPECTACIN)

BY

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In the years immediately following the introduction of penicillin for the treatment of syphilis, comprehensive and continuous evaluations of treatment were conducted, first to establish the optimal dosage requirements for syphilis (Merrell, 1949; Rider, 1949; Bauer, 1951), and later to determine the relative efficacy of various penicillin preparations as they were introduced (Cutler, Olansky, and Price, 1955; Smith and Price, 1960). In a more modest manner other antibiotics for syphilotherapy were also evaluated (Olansky and Garson, 1958). In general these studies terminated with the rapid drop in incidence of syphilis in the early 1950s.

On the basis of these early studies the United States Public Health Service currently recommends the following schedules for the treatment of early syphilis.

- (1) Benzathine penicillin G, 2·4 million units total (1·2 million units in each buttock) by intramuscular injection.
- (2) Procaine penicillin G in oil with aluminum monostearate (PAM), 4·8 million units total, usually given as 2·4 million units at the first session and 1·2 million units in each of two subsequent injections 3 days apart.
- (3) Aqueous procaine penicillin G, 600,000 units daily for 8 days to a total 4·8 million units.

Or for alternate therapy when penicillin sensitivity precludes the use of penicillin:

- (4) Erythromycin, 20–30 g. given orally over a period of 10 to 15 days.
- (5) Tetracycline, 30–40 g. given orally over a period of 10 to 15 days.

Although there has been little evidence to indicate that the *Treponema pallidum* is any less susceptible to penicillin now than when it was introduced in 1943, the sharp increase in incidence of syphilis over the past few years not only suggested that it was time to re-evaluate our methods of treatment but also provided the cases necessary for such an undertaking.

In July, 1965, the Venereal Disease Program initiated an evaluation to establish the current comparative effectiveness of schedules now recommended by the Public Health Service for the treatment of early syphilis and to determine the efficacy of a new injectable antibiotic, spectinomycin (actinospectacin, Trobicin). Clark and Yobs (1963, 1964, 1966 a, b) have extensively studied the effects of spectinomycin in experimental rabbit syphilis. They have reported that a daily injection of 1·0 mg./kg. for 7 days (total, 7 mg./kg.) was curative in experimental early lesion rabbit syphilis (1966a). Further, unpublished data by these authors (1966b) indicate that seven single daily injections of 0·5 mg./kg. are also curative (total 3·5 mg./kg.).

Single doses of 1·2 to 1·6 g. spectinomycin have been shown by Willcox (1962), Laird and Taylor (1962), and Tiedemann, Hackney, and Price (1965) to be an effective treatment for gonorrhoea in males. In a recent study of spectinomycin in gonorrhoea in females by Lucas, Price, Thayer, and Schroeter (1967), a single injection of 4 g. was found comparable in efficacy to 2·4 million units aqueous procaine penicillin G.

In view of the lack of toxicity and paucity of adverse reactions associated with spectinomycin and its high degree of efficacy in experimental syphilis, it was felt that an evaluation in syphilotherapy was indicated.

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Nine city or county health departments* agreed to co-operate in the study.

Selection of Cases and Examination of Patients

Selection of cases is limited to darkfield-positive primary or secondary syphilis and re-infected patients meeting these criteria are accepted. Consideration is also given to permanence of residence and distance from the clinic, and the patients' intelligence and willingness to co-operate in the study.

The initial examination of the patient, in addition to the darkfield, includes a complete physical examination and serological tests for syphilis. Whole blood specimens (for both pre- and post-treatment examinations) are submitted to the Venereal Disease Research Laboratory, Atlanta, for the VDRL slide test and treponemal antigen tests. Daily darkfield examinations are performed on patients treated by schedules requiring daily injections.

Follow-up examinations, including physical inspection and serological tests, are scheduled monthly for the first year and quarterly for the second year. Only one spinal fluid examination is requested, to be performed at the end of observation—2 years after treatment. To co-ordinate the study and to assure adequate post-treatment observation, special investigators have been assigned to each of the co-operating clinics.

Schedules of Treatment

Seven schedules of treatment are being evaluated. These include the five currently recommended by the Public Health Service, employing for the erythromycin and tetracycline schedules the minimum specified dosage and duration (*i.e.* 20 and 30 g. respectively in 10 days); and two schedules utilizing spectinomycin sulphate, one of 32 g. administered in a dosage of 4 g. daily and one of

16 g. in a dosage of 2 g. daily for 8 days. Clinics have been requested to rotate these seven schedules, either by patient or weekly, depending upon clinic volume.

The erythromycin previously evaluated by the Public Health Service (Brown, Simpson, Moore, Price, and Weinstein, 1963) and upon which the recommended schedule is based was propionyl erythromycin lauryl sulphate. Cholestatic hepatitis, however, has been reported after prolonged usage of this preparation. Although it was anticipated that it would be somewhat less effective because of the lower blood levels produced, the base form of erythromycin was therefore selected for this evaluation.

Drugs were secured by the Venereal Disease Program and distributed to the co-operating clinics so that identical preparations would be evaluated by the participants.

Results of Treatment

This report includes the results of treatment during the first year of observation. The statistical method of analysis is that described by Iskran, Bowman, and Donohue (1948) for evaluating antisyphilitic therapy. Since the critical period for the occurrence of relapse or re-infection covers roughly the 3rd to the 9th month following treatment, these preliminary data cover a period sufficiently long to give a reliable comparison of the *relative efficacy* of the various treatment schedules. The determination of *cure*, however, must await more prolonged observation.

In Table I the cumulative re-treatment rates (including both relapse and re-infection) at the 3rd, 6th, 9th, and 12th month of observation are shown by schedule for total cases treated and for those with

TABLE I
COMPARATIVE EFFECTIVENESS OF VARIOUS SCHEDULES OF TREATMENT FOR EARLY SYPHILIS

Series	Schedule of Treatment	Total Cases Treated	Third Month			Sixth Month			Ninth Month			Twelfth Month		
			Cases Observed	Re-treated*		Cases Observed	Re-treated*		Cases Observed	Re-treated*		Cases Observed	Re-treated*	
				Number	Cumulative Percentage		Number	Cumulative Percentage		Number	Cumulative Percentage		Number	Cumulative Percentage
All Cases Including Previous Infections	Spectinomycin—32 grams	44	32	0	0.0	30	4	12.5	21	8	28.7	15	8	28.7
	Spectinomycin—16 grams	45	38	1	2.3	31	6	17.0	21	10	32.3	11	11	38.5
	Aq. proc. pen.—4,800,000 u.	37	25	0	0.0	19	1	5.3	13	1	5.3	2	1	5.3
	Benzathine pen.—2,400,000 u.	70	50	0	0.0	35	2	4.6	23	2	4.6	14	2	4.6
	PAM—4,800,000 u.	71	44	3	6.2	28	3	6.2	16	3	6.2	5	3	6.2
	Erythromycin—20 grams	71	42	2	4.8	29	8	24.2	22	9	27.6	12	9	27.6
	Tetracycline—30 grams	67	46	0	0.0	30	2	5.6	22	2	5.6	10	2	5.6
First Infections Only	Spectinomycin—32 grams	43	31	0	0.0	29	4	12.9	20	8	29.9	16	8	29.9
	Spectinomycin—16 grams	40	34	0	0.0	29	5	16.3	18	9	33.4	10	9	33.4
	Aq. proc. pen.—4,800,000 u.	36	24	0	0.0	18	1	5.6	12	1	5.6	2	1	5.6
	Benzathine pen.—2,400,000 u.	60	44	0	0.0	31	2	5.2	20	2	5.2	13	2	5.2
	PAM—4,800,000 u.	66	39	3	6.8	24	3	6.8	13	3	6.8	4	3	6.8
	Erythromycin—20 grams	66	38	2	5.3	26	7	23.6	21	8	27.4	11	8	27.4
	Tetracycline—30 grams	52	34	0	0.0	21	0	0.0	16	0	0.0	8	0	0.0

*Treatment failure or re-infection re-treated in this period or earlier.

first infections only. In general, patients who have previously been infected constitute a group which may be classified as "syphilis prone"; they are also a group whose serological response to treatment may be expected to follow a pattern somewhat different from previously untreated cases.

With the possible exceptions of the 16 g. spectinomycin schedule, which decreased from 38.5 to 33.4 per cent., and the tetracycline schedule, which decreased from 5.6 to 0.0 per cent., only very minor changes resulted from the exclusion of previously infected cases. Therefore, regardless of the group analysed, it is obvious that the two spectinomycin schedules and the erythromycin schedule are unsatisfactory for the treatment of early syphilis; that the three penicillin schedules are approximately equal in efficacy; and that the tetracycline schedule is at least as efficacious as the penicillin schedules.

The first indication that spectinomycin was less effective than penicillin was seen in the length of time required for the darkfield to become negative. 84 per cent. of the patients treated with aqueous procaine penicillin were darkfield-negative on the second day of observation after one injection and the remainder were negative on the 3rd day. Only 44 per cent. of the spectinomycin-treated patients were negative on the second day of observation and 18 per cent. required 4 days or more for the treponemes to disappear. One patient on the 16 g. schedule was still positive on the 8th day of observation after receiving five injections of spectinomycin. This patient was considered to be a treatment failure and was then re-treated with benzathine penicillin G.

The post-treatment observation rate (based on total observation period rather than number of scheduled observations completed) is only 60 per cent. Apparently less effort has been expended in keeping the penicillin-treated patients under observation—the rates for these three schedules range from 48 to 60 per cent.; for the four schedules employing other antibiotics, the post-treatment observation rates range from 64 to 69 per cent.

Another factor which may cause a bias in results is the distribution of cases by stage of syphilis. Only 32 patients with sero-negative primary syphilis are included in the evaluation and all made a satisfactory response to treatment. These cases have been omitted from the Figure, in which only the results of treatment in previously uninfected sero-positive primary syphilis and secondary syphilis are compared. Because the number of cases included in the evaluation is small and there is no appreciable difference in re-treatment rates between the two spectinomycin schedules or among the three penicillin schedules, the results are shown by therapeutic agent rather than by schedule of treatment.

The data in the Figure (opposite) substantiate the conclusions drawn from Table I, *i.e.* that spectinomycin and erythromycin, in the dosages employed, are inadequate for sero-positive primary or for secondary syphilis; and that tetracycline, at either stage, is as effective as penicillin. Because of the small number of cases involved, these provisional data on tetracycline are most subject to change. Only 52 were previously uninfected cases and of these 21 were in the sero-positive primary stage and 27 in the secondary. The penicillin-treated group includes 89 sero-positive primary cases and 48 secondary cases.

As predicted by the similarity of results between the 32 g. and 16 g. schedules, an analysis of the spectinomycin-treated cases by body-weight dosage proved unrewarding. The cumulative re-treatment rate for patients receiving less than 350 mg./kg. is 34.9 per cent., and for those receiving more than 350 mg./kg. it is 27.1 per cent. (Table II.) Only in secondary syphilis does the larger dosage seem to have an advantage, but here the number of cases is too small to be meaningful. Since two schedules were involved (16 and 32 g.), the dosage as determined by body weight has a wide range—from 141 to 563 mg. The range is similar for patients requiring further treatment—from 188 to 510 mg. These dosages are

TABLE II
RESULTS OF TREATMENT WITH SPECTINOMYCIN AND ERYTHROMYCIN WHEN DOSAGE IS RELATED TO BODY WEIGHT OF PATIENT

Drug	Dosage by Weight of Patient	Primary Syphilis		Secondary Syphilis		Total	
		Total Cases Treated	Cumulative Percentage Re-treated	Total Cases Treated	Cumulative Percentage Re-treated	Total Cases Treated	Cumulative Percentage Re-treated
Spectinomycin	< 350 (141-349) mg./kg.	23	26.4	16	45.8	39	34.9
	> 350 (352-563) mg./kg.	23	29.9	15	23.1	38	27.1
Erythromycin	< 300 (216-294) mg./kg.	25	34.6	6	*	31	40.1
	> 300 (304-441) mg./kg.	13	14.3	20	11.1	33	13.1

*Not shown because of small number of cases treated.

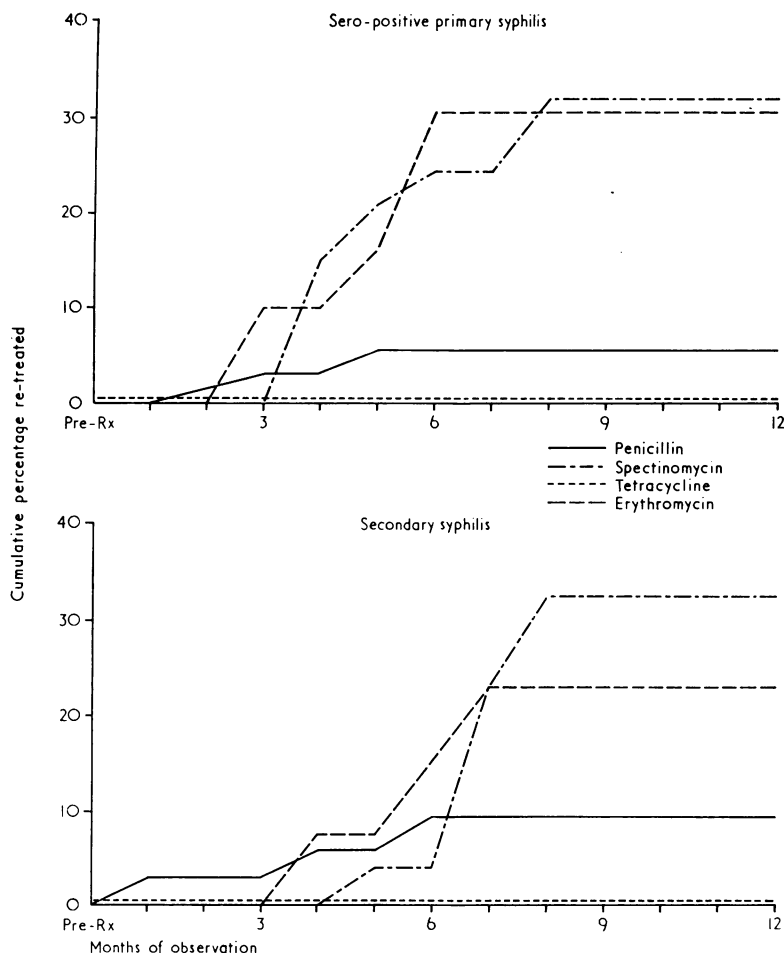


FIGURE.—Cumulative re-treatment rates during 12 months' observation by antibiotic administered (Previously untreated cases).

far in excess of the previously-discussed schedules shown to be effective in experimental syphilis.

On the other hand, the poor results among patients treated with erythromycin appear to be definitely related to body-weight dosage. The re-treatment rate among patients receiving less than 300 mg./kg. is more than triple that among those receiving more than 300 mg./kg. This is in spite of the fact that the majority of the lower dosage cases were in the primary stage while the majority of the higher dosage cases were in the secondary stage. Furthermore, the range in dosage among patients requiring additional treatment is 238 to 314 mg./kg./body weight. This maximum dosage of 314 mg. falls at the low end of the scale for the group of patients

treated with more than 300 mg./kg./body weight.

It was anticipated, as discussed previously, that the erythromycin base would be less effective than propionyl erythromycin lauryl sulphate. However, had we selected for evaluation the maximum recommended dosage of 30 g. rather than the minimum of 20 g., all patients treated with erythromycin would have received more than the maximum body-weight dosage resulting in treatment failure, *i.e.* over 314 mg./kg.

Reactions to Treatment

Among a total of 429 cases studied, reactions to treatment were reported in 38 (8.9 per cent.). Herxheimer reactions comprised 4.9 per cent. of

this rate. The highest rates were noted in patients treated with spectinomycin—20.0 per cent. for the 32 g. schedule and 21.3 per cent. for the 16 g. schedule. Unquestionably there is closer observation and reporting of reactions following the use of a new drug, as well as a greater exercise of caution in its administration. Treatment was discontinued in one instance in which symptoms suggest a probable Herxheimer reaction—chills and fever (104° F. temperature) and oedematous penile lesions following the first and second injections of spectinomycin, with epistaxis accompanying the fever after the second injection.

Although the majority of reactions reported were of a minor nature, at least one patient on each schedule (with the exception of the single injection of benzathine penicillin G) had treatment discontinued or changed because of reactions. These were as follows:

Schedule 1—Spectinomycin 32 g. Discomfort at site of injections and aching down back of thighs, with nausea and dizziness. Treatment changed to penicillin on the 12th day after five injections of spectinomycin.

Schedule 2—Spectinomycin 16 g. Two patients: one with the probable Herxheimer discussed above; the other with urticaria one hour after the second injection.

Schedule 3—Aqueous procaine penicillin G Urticaria on the 10th day after seven injections.

Schedule 5—Procaine penicillin G in oil Generalized pruritus on the 4th day after the 2nd injection.

Schedule 6—Erythromycin Perianal itching and dermatitis extending to the scrotum, penis, and thighs, on the 2nd day of treatment.

Schedule 7—Tetracycline Gastrointestinal reaction starting on 3rd day of treatment and continuing for 4 days. Treatment completed with penicillin.

Summary and Conclusions

- (1) Preliminary data on a co-operative evaluation of treatment for early syphilis are presented.
- (2) Cumulative re-treatment rates during a one-year observation period are compared for seven schedules evaluated.
- (3) These data indicate that spectinomycin is an unsatisfactory drug for the treatment of syphilis.
- (4) A dosage of 20 g. of the base form of erythromycin is inadequate for the treatment of early syphilis; a body-weight analysis suggests that a 30 g. dosage would be effective.
- (5) Tetracycline, in a 30 g. dosage, compares favourably with the penicillin schedules evaluated.
- (6) A comparison of the relative efficacy of penicillin now and 20 years ago must await more prolonged observation.

- (7) No serious reactions to treatment were observed among the 429 patients included in the evaluation to date.

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Une évaluation des traitements de la syphilis précoce résultant d'une coopération d'efforts. Un rapport préliminaire se référant spécialement au sulfate de Spectinomycine (Actinospectacine)

RÉSUMÉ ET CONCLUSIONS

- (1) Les données préliminaires au sujet d'une évaluation des traitements de la syphilis précoce résultant d'une coopération d'efforts sont présentées.
- (2) Les taux des traitements cumulatifs pendant une période d'observation d'une année sont comparés pour les sept plans de traitement.
- (3) Ces données indiquent que la spectinomycine n'est pas un médicament efficace pour le traitement de la syphilis.
- (4) Un dosage de 20 g. d'érythromycine (basique) n'est pas suffisant pour le traitement de la syphilis précoce; une analyse suggère que par rapport au poids du malade un dosage de 30 g. serait effectif.
- (5) La tétracycline en dosage de 30 g. se compare favorablement à la posologie de la pénicilline dans les différents plans de traitement qui ont été évalués.
- (6) Une comparaison entre l'efficacité relative de la pénicilline aujourd'hui et celle d'il y a vingt ans devra attendre une plus longue étude.
- (7) Aucune réaction grave n'a été observée pendant le traitement jusqu'à ce jour chez les 429 malades inclus dans cette évaluation.